Bone 79 (2015) 259–266

Contents lists available at ScienceDirect

Bone

journal homepage: www.elsevier.com/locate/bone

TBS reflects trabecular microarchitecture in premenopausal women and men with idiopathic osteoporosis and low-traumatic fractures

Christian Muschitz [a,*,1], Roland Kocijan [a,1], Judith Haschka [a], Dieter Pahr [b], Alexandra Kaider [c], Peter Pietschmann [d], Didier Hans [e], Gabriela Katharina Muschitz [f], Astrid Fahrleitner-Pammer [g], Heinrich Resch [a]

[a] St. Vincent Hospital, Medical Department II, Academic Teaching Hospital of the Medical University of Vienna, Austria
[b] Institute of Lightweight Design and Structural Biomechanics, Vienna University of Technology, Vienna, Austria
[c] Center for Medical Statistics, Informatics and Intelligent Systems, The Medical University of Vienna, Austria
[d] Department of Pathophysiology and Allergy Research, Center for Pathophysiology, Infectiology and Immunology, Medical University of Vienna, Austria
[e] Center of Bone Diseases, Lausanne University Hospital Switzerland
[f] Division of Plastic and Reconstructive Surgery, Department of Surgery, Medical University of Vienna, Vienna, Austria
[g] Department of Internal Medicine, Division of Endocrinology and Metabolism, The Medical University of Graz, Austria

ARTICLE INFO

Article history:
Received 10 April 2015
Revised 19 May 2015
Accepted 10 June 2015
Available online 16 June 2015

Edited by Robert Recker

Keywords:
Idiopathic osteoporosis
Bone microarchitecture
Trabecular bone score
Bone μCT
Bone turnover marker

ABSTRACT

Transiliac bone biopsies, while widely considered to be the standard for the analysis of bone microstructure, are typically restricted to specialized centers. The benefit of Trabecular Bone Score (TBS) in addition to areal bone mineral density (aBMD) for fracture risk assessment has been documented in cross-sectional and prospective studies. The aim of this study was to test if TBS may be useful as a surrogate to histomorphometric trabecular parameters of transiliac bone biopsies. Transiliac bone biopsies from 80 female patients (median age 39.9 years — interquartile range, IQR 34.7; 44.3) and 43 male patients (median age 42.7 years — IQR 38.9; 49.0) with idiopathic osteoporosis and low traumatic fractures were included. Micro-computed tomography values of bone volume fraction (BV/TV), trabecular thickness (Tb.Th), trabecular number (Tb.N), trabecular separation (Tb.Sp), structural model index (SMI) as well as serum bone turnover markers (BTMs) sclerostin, intact N-terminal type 1 procollagen propeptide (P1NP) and cross-linked C-telopeptide (CTX) were investigated. TBS values were higher in females (1.282 vs 1.169, $p < 0.0001$) with no differences in spine aBMD, whereas sclerostin levels (45.5 vs 33.4 pmol/L) and aBMD values at the total hip (0.989 vs 0.971 g/cm^2, $p < 0.001$ for all) were higher in males. Multiple regression models including: gender, aBMD and BTMs revealed TBS as an independent, discriminative variable with adjusted multiple R^2 values of 69.1% for SMI, 79.5% for Tb.N, 68.4% for Tb.Sp, and 83.3% for BV/TV. In univariate regression models, BTMs showed statistically significant results, whereas in the multiple models only P1NP and CTX were significant for Tb.N. TBS is a practical, non-invasive, surrogate technique for the assessment of cancellous bone microarchitecture and should be implemented as an additional tool for the determination of trabecular bone properties.

Introduction

Osteoporosis is a skeletal disorder characterized by low bone strength and increased low-traumatic fracture risk. Areal bone mineral density (aBMD) measured by dual-energy X-ray absorptiometry (DXA) is considered the standard technique for the diagnosis of osteoporosis [1]. Patients who sustain osteoporosis-related low-traumatic fractures have reduced bone mass as well as alterations in bone microstructure. It is worth noting that most low-traumatic fractures occur in patients with osteopenia or normal aBMD, suggesting that aBMD is of limited benefit for fracture risk prediction. Furthermore, there is a considerable overlap in aBMD values of patients with and without fractures [2,3]. As a result, aBMD alone is not a reliable indicator for fracture risk. Several factors are known to influence bone strength and fracture risk, including the anatomic dimensions of cortical bone, the microstructure of trabecular bone, microdamages, changes in material properties as well as bone mineralization and turnover [2]. To address these issues, advanced analytical methods have been established to assess cortical and trabecular microarchitecture individually. Transiliac bone biopsies, despite their invasiveness, are considered to be the current best method for microstructural analysis. In clinical practice,

* Corresponding author at: St. Vincent Hospital Vienna, Medical Department II, Medical University of Vienna, Austria, Stumpergasse 13, A, 1060 Vienna, Austria. Fax: +43 1 59988 4041.
E-mail address: christian.muschitz@bhs.at (C. Muschitz).
[1] CM and RK contributed equally to this manuscript.

http://dx.doi.org/10.1016/j.bone.2015.06.007
8756-3282/

performing transiliac biopsies is limited and used only for exceptional and complicated patient cases. Beyond being invasive, transiliac bone biopsies are costly and time-intensive procedures [4]. Another factor worth considering is the ongoing discussion as to whether or not the iliac crest as a non–weight-bearing bone site is representative for microstructure elsewhere in the body. Among non-invasive techniques, high-resolution peripheral quantitative computed tomography (HR-pQCT) and magnetic resonance imaging (MRI) allow direct measurements of the bone microarchitecture. These methods remain impractical for routine screening due to high costs, the availability of devices and the lack of validation studies. In light of these difficulties, trabecular bone score (TBS), a greyscale textural analysis that estimates trabecular microarchitecture from the anterior/posterior (AP) lumbar spine DXA, has been established [5,6]. The benefit of TBS in addition to aBMD for fracture risk assessment has been documented in several cross-sectional and prospective studies [6–8]. On the structural level of bone tissue, significant correlations have been identified between TBS and 3D parameters of bone microarchitecture independent of any correlation between TBS and aBMD. However, the analysis was performed in human cadaver vertebrae [9,10].

The aim of the present study was to test whether or not a non-invasive 3D imaging technique, such as TBS assessed by spinal DXA, would be useful as a surrogate for morphometric trabecular parameters of transiliac bone biopsies.

The primary objective of this study was to evaluate associations between spine TBS and trabecular microarchitectural parameters of transiliac bone biopsies (SMI, Tb.N, Tb.Sp, BV/TV) in treatment-naïve premenopausal women and similarly aged men with low-traumatic fractures.

Secondary objectives were to evaluate the role of (i) TBS and serum bone turnover markers of osteocyte, osteoblast and osteoclast activity (sclerostin, P1NP, CTX) and (ii) gender-specific differences in this context in young patients with low-traumatic fractures.

Materials and methods

Patients

In this two-center cross-sectional study, between January 2005 and December 2014, all eligible patients with idiopathic osteoporosis were recruited at the outpatient clinic of the Medical Department II for Rheumatology and Bone Diseases, St. Vincent Hospital Vienna (Austria) and the Department of Internal Medicine, Division of Endocrinology and Metabolism, the Medical University of Graz, Austria. The study was approved by the local ethics committee. All patients signed a written informed consent form prior to any study-related procedures. Medical history, current medications and previous fractures (including trauma history) were recorded. Men and premenopausal women were included if they had sustained at least one low-traumatic vertebral or non-vertebral fracture and were otherwise healthy. Low-traumatic fractures were defined as fractures sustained after a minor injury or without any identifiable trauma that would not typically result in a bone fracture [11]. Vertebral fracture status was analyzed by antero-posterior and lateral digital X-ray studies of the thoracic and lumbar spine (Digital Diagnost, Philips, Best, the Netherlands). The images were evaluated by two independent, experienced radiologists using Genant's semi-quantitative approach [12]. Peripheral fractures were self-reported and assessed by questionnaire. Patients were excluded if they had any prior antiresorptive therapy (bisphosphonates or denosumab, and raloxifene), or any anabolic therapy (teriparatide, PTH 1-84), as well as strontium ranelate. Further exclusion criteria were any systemic or local inflammatory or autoimmune disease, any type of acute or chronic liver disease, type 1 or type 2 diabetes mellitus, hypo- or hyperthyroidism, alcohol intake > 2 IU/day, smoking > 10 cigarettes/day, coronary heart disease, cardiomyopathy, spondyloarthritis, osteogenesis imperfecta, depression, eating disorders, chronic malnutrition or malabsorption, hemochromatosis, chronic obstructive pulmonary disease, Cushing's disease, estrogen deficiency, body mass index ≤20 kg/m2, any stage of hyperparathyroidism, hypoparathyroidism, a 25-hydroxyvitamin D deficiency ≤20 ng/mL, serum calcium or phosphate levels outside range of normal, any stage of chronic kidney disease, ongoing or a history of immunosuppression, any medical history of malignancy and/or chemotherapy/radiation therapy. None of the patients received oral contraceptives, or any hormone therapy including estrogen or testosterone substitution. A physical examination was performed and body weight and patient height were compiled.

Laboratory analyses

Fasting blood samples were drawn from all patients between 8:00 and 10:00 a.m. Samples were immediately cooled, centrifuged and stored at −70 °C. Routine blood and urine analyses included whole blood count and the following lab parameters: serum potassium, sodium, calcium, phosphate, intact parathyroid hormone (iPTH), 25-hydroxyvitamin D, thyroid-stimulating hormone (TSH) as well as parameters of kidney and liver function. All parameters were measured on the Abbott Architect platform. Bone markers were measured using electrochemiluminescence immunoassays (ECLIA): cross-linked C-telopeptide (CTX), N-MID Osteocalcin (OCN), intact N-terminal type 1 procollagen propeptide (P1NP); Immunodiagnostic System IDS using aiSYS device (IDS-iSYS). Sclerostin was quantitatively determined from serum by an enzyme immunoassay (EIA) kit (Biomedica, Vienna, Austria). Intra-assay coefficient of variation (CV) was 5%–6% for sclerostin, 2.1%–4.9% for CTX, 2.6%–3.0% for P1NP, 1.1%–3.7% for iPTH and 5.5%–7.1% for 25-hydroxy vitamin D.

Transiliac bone biopsies

The mean time from low traumatic fracture to transiliac bone biopsy was ≥6 months. Using a Bordier-type trephine, all biopsies were carried out under sterile conditions in a local operating room. The biopsy cylinder (inner diameter = 7.5 mm) was used for subsequent structural analyses and was placed in 70% ethanol. For this study, only microstructural parameters assessed by micro-CT were included. The biopsies were scanned with an established micro-CT scanner (μCT 40, SCANCO Medical AG, Brüttisellen, Switzerland) using the settings of 70 kVp, 114 mA, 200 ms integration time, 2,048 × 2,048 pixels image matrix and 18 μm isotropic spatial resolution. After applying a Gaussian filter ($\sigma = 1.2$, support = 2), an optimal threshold was computed by thresholding the individual bone cubes using the single-level threshold of IPL (SCANCO Medical AG, Brüttisellen, Switzerland) and averaging the threshold values for each region. After segmentation, unconnected bone regions were removed from the scans, bone volume fraction (BV/TV, %), trabecular thickness (Tb.Th, mm), trabecular number (Tb.N, mm_1), trabecular separation (Tb.Sp, mm), degree of anisotropy (DA, unitless) and structural model index (SMI) reflecting the rod- versus plate-like nature of the structure (0 = plate-like; 3 = rod-like) were assessed by using IPL (SCANCO Medical AG, Brüttisellen, Switzerland).

Trabecular bone score (TBS) measurement and areal bone mineral density (aBMD)

The DXA files of the study population were digitally exported and the raw data was extracted to a specific workstation for trabecular bone score (TBS) calculation using the latest version of TBS iNsight software (Medimaps SA, France). TBS was calculated as a mean value of the measurement for vertebrae L1–L4 exactly at the same ROI as spine aBMD. TBS is a unitless index that characterizes bone microstructure obtained by macroscopic representation and can be applied to any X-ray image including DXA images by quantifying local variations in grey level. It uses experimental variograms